Curr Rheumatol Rep (2015) 17:51
DOI 10.1007/s11926-015-0526-z

HCV Treatments and Their Integration Into Rheumatology

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Abstract Hepatitis C virus (HCV) has been associated with distinct rheumatic syndromes including arthritis, sialadenitis, and cryoglobulinemic vasculitis (CV). The therapy of these HCV-associated syndromes includes antiviral therapy with or without the addition of immunosuppressives while clinical response is mainly seen in patients who clear the virus after antiviral therapy. Despite significant therapeutic advances, existing antiviral therapies with interferon-a (IFNa)-based schemes achieve viral eradication only in approximately half the patients. Recently, oral antivirals that target specific HCV proteins referred as direct acting antivirals (DAAs) have been developed and approved. Short-term (12–24 weeks) combination schemes with or without IFN ("IFN-free" regimens) including these inhibitors clear the virus in more than 90 % of treated patients. Here, we review current therapeutic options in HCV-associated rheumatic syndromes and the potential role of the newly available antivirals in an integrated therapeutic approach.

Keywords Hepatitis C virus · HCV · Viral hepatitis · Disease modifying anti-rheumatic drugs · DMARDs · Biologic agents · Cryoglobulinemic vasculitis · Interferon-a · Ribavirin · Protease inhibitors · Rituximab · Therapy · Arthritis · Sialadenitis

This article is part of the Topical Collection on *Infections and Arthritis*

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Introduction

Hepatitis C virus (HCV) infection remains one of the most common chronic viral infections worldwide with 170 million people infected [1]. Over the last 25 years, since the initial identification of the virus and the widespread implementation of screening programs, there has been an escalating effort to better understand the pathogenesis, natural course, and complications (hepatic and extra-hepatic) of this chronic infection and moreover to develop more efficacious antiviral therapies that could eradicate the virus. The recent breakthrough advances in the treatment of chronic hepatitis C have raised expectations that the disease is finally curable and the goal of eradicating this infection in the foreseeable future appears feasible.

In this review, we will review the main rheumatic syndrome associated with chronic HCV infection and their therapy in light of the recent advances in the therapy of HCV infection.

HCV-Related Rheumatic Diseases and Their Therapy

Chronic HCV infection is the cause of distinct rheumatic syndromes such as inflammatory arthritis (resembling rheumatoid arthritis—RA), an autoantibody negative sialadenitis (resembling primary Sjögren's syndrome), and more importantly an immune-complex mediated systemic small vessel vasculitis, i.e., cryoglobulinemic vasculitis (CV). For these HCV-related syndromes, HCV eradication can lead to significant improvement or even cure of these associated syndromes.

Published online: 26 June 2015

Arthritis

Clinical Features

HCV has been associated with arthralgias or less frequently with an inflammatory arthritis in the form of an oligo- or polyarthritis that could be part of the mixed cryoglobulinemia syndrome (see below) or appearing in patients without clinical manifestations of cryoglobulinemia [2, 3]. HCV-related arthritis is usually an anti-CCP negative, non-erosive oligo- or polyarthritis (RA-like) that develops in a small proportion of patients with chronic hepatitis C (<5 %) [2]. In a limited number of patients where synovial biopsies were available, a mild synovitis was noted [2].

Therapy

Its clinical course is usually benign and arthritis is treated with low-dose corticosteroids (<10 mg/day) and disease-modifying anti-rheumatic drugs (DMARDs) such as hydroxychloroquine. Antiviral therapy with interferon (IFN)-based therapeutic schemes have led to clinical improvement in older studies [4].

Sialadenitis

Clinical Features

A mild, usually autoantibody (anti-Ro/La) negative form of sialadenitis characterized by a predominantly T-cell infiltration (CD4 and CD8) of the salivary glands in a peri-capillary fashion has been described in chronically infected HCV patients [5]. Its frequency in unselected large populations of HCV-infected patients varies widely depending on the criteria used for its diagnosis (clinical vs. histological) [6]. Although clinical manifestations such as sicca symptoms have been reported in <10 % of HCV infected patients [7], salivary gland biopsies show abnormal findings in approximately half of patients [5]. It should be also noted that approximately half of the patients with HCV-associated sialadenitis have circulating cryoglobulins and low complement levels (compared to ~10 % of patients with primary Sjögren's syndrome) and approximately 20 % clinical manifestations of vasculitis (compared to 12 % of patients with primary Sjögren's) [6], emphasizing that in a significant proportion of patients sialadenitis is part of the HCV-related mixed cryoglobulinemia syndrome. Such patients with cryoglobulinemia and sialadenitis run a higher risk for development of lymphoma either in the salivary glands or the liver [8]. Whether or not HCV is directly (through viral replication in the salivary glands) or indirectly involved to the development of sialadenitis has not been clearly determined so far [5].

Therapy

Data regarding the efficacy of antiviral treatment in such patients are limited [9–11, 12••]. In an older study, Cacoub et al. observed a similar decrease in sicca symptoms both in sustained virological responders and non-responders to antiviral therapy as well as to untreated patients [9] while Isaacs et al. recently did not observe any change in the frequency of xerostomia and xeropthalmia after treatment with pegylated IFN and ribavirin [11]. On the contrary, Doffoël-Hantz et al. observed a 50 % improvement in sicca symptoms in patients treated with interferon and ribavirin (although no control group of untreated patients was available for comparison) [10]. Furthermore, in a large prospective, open-label study from Italy, approximately 61 % (17/28) of patients with sicca symptoms occurring as part of the mixed cryoglobulinemia syndrome demonstrated significant improvement of their symptoms after viral clearance was achieved with antiviral therapy [12••].

HCV-Associated Cryoglobulinemic Vasculitis (CV)

Clinical Features

Among the various rheumatological manifestations associated with chronic hepatitis C, HCV-associated CV is the best documented and studied so far. According to the definitions by the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC12), CV is defined as a "vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) and associated with serum cryoglobulins. Skin, glomeruli, and peripheral nerves are often involved"; HCV-associated CV has been categorized in the group of "vasculitis with probable etiology" [13]. More recently, specific criteria for CV have been developed [14] and validated [15].

Although cryoglobulins are frequently detected in patients with chronic hepatitis C (12–56 %), HCV-associated CV occurs in a small proportion of patients (<3 %) [16]. In general, patients with HCV-associated CV have a longer disease duration and a higher rate of underlying cirrhosis (29–40 %) [12••, 17, 18] compared to HCV patients with asymptomatic cryoglobulinemia or without cryoglobulins [12••].

The clinical characteristics of patients with HCV-associated CV have been well described in recent reviews [16, 19•, 20]. The most commonly involved organs are the skin (purpura, ulcers, necrotic lesions, Raynaud's phenomenon), nerves (peripheral neuropathy, mononeuritis multiplex), joints (arthralgias >> arthritis), kidneys (membranoproliferative glomerulonephritis), and salivary glands (sicca syndrome). Less frequently, the heart (heart failure), gastrointestinal system (ischemia), CNS (ischemic lesions), and lungs (mild fibrosis) can be involved.

A number of long-term follow-up studies have described its clinical course [21–23]. In approximately one third of the patients, the disease follows an aggressive course [21] while in 15 % life-threatening complications can occur [24]. Overall, the 10-year survival rate ranges between 56 and 80 %[21–23]; baseline factors associated with a poor prognosis include advanced liver fibrosis, male sex, and advanced age [21, 22].

Therapy

Traditionally, the therapy of HCV-associated CV includes antiviral therapy and/or immunosuppressive agents based on the severity of the vasculitis process [16, 25, 26]. So far, there have not been any randomized controlled studies comparing the efficacy of different treatment approaches in this disease.

Antiviral Therapy Antiviral regimens have been given either as monotherapy or in combination with immunosuppressive agents. A number of studies have shown that whenever sustained virological response (SVR—defined as a negative serum HCV RNA 3–6 months after completion of therapy) is achieved by antiviral therapy, significant clinical improvement of the HCV-associated CV occurs. The improvement of antiviral therapies against HCV over the last 25 years has contributed to the better care and survival of patients with HCV-associated CV.

IFNa Monotherapy

Initial trials with IFNa monotherapy in patients with HCV-associated CV demonstrated good initial clinical responses, but these were followed by relapses since SVR was obtained only in 7–10 % of patients [27]. In a recent meta-analysis of 11 studies of 235 patients with symptomatic HCV-associated CV treated with IFNa monotherapy, Fabrizi et al. showed a 15 % SVR rate that correlated well with clinical response [28].

IFNa and Ribavirin

In 1998, the addition of ribavirin to the standard IFNa regimen increased the SVR rate to approximately 25 % that increased furthermore to 40–50 % with the substitution of standard by pegylated (Peg)-IFNa in 2001 [1]. This combination has been the standard of care for patients with chronic hepatitis C over the last 15 years.

A number of open-label studies have shown that this combination was also efficacious in patients with HCV-associated CV [16, 19•] with an SVR and clinical response occurring in almost half the patients treated with Peg-IFNa and ribavirin [29–34]. The results of the individual studies were confirmed by a recent meta-analysis that found a 52 % SVR rate in 300 patients with symptomatic HCV-associated CV treated with Peg-IFNa and ribavirin [35]. These results are not much different from the SVR achieved in HCV patients without cryoglobulinemia [1]. Nevertheless, in a recent open-label cohort study from Italy, patients with symptomatic mixed cryoglobulinemia had a lower response to antiviral therapy compared to those without cryoglobulinemia (52 vs. 61 %) [12••].

Aside from its poor response in half of the patients with symptomatic HCV-associated CV, IFNa-based antiviral regimens had certain limitations in their use as first-line treatment in such patients. In most of the open-label trials, patients who were included did not have severe vasculitis (i.e., renal failure, severe neuropathy, etc.) and most of the improvement was seen in patients with purpura, arthralgias/arthritis, and mild neuropathy. Furthermore, these medications need extra caution when used in patients with renal dysfunction; ribavirin is contraindicated for creatinine clearance (CrCl) less than 50 ml/min while the dose of Peg-IFNa has to be reduced for CrCl less than 60 ml/min [19•].

Moreover, it is well known that IFNa can induce an exacerbation of the underlying CV that could be life threatening [26]. In a recent study, 8/22 patients with HCV-associated cryoglobulinemia demonstrated an initial increase in cryocrit levels 1 month after treatment with Peg-IFNa and ribavirin [36]. Other side effects that limit the use of IFNa in patients with HCV-associated CV include bone marrow suppression, “flu-like” symptoms, and psychiatric side effects.

Based on the available data, this combination is suggested by most experts as the first-line treatment for patients with HCV-associated CV and mild to moderate disease activity (mainly skin and joint disease) [16, 19•, 25].

Direct Acting Antivirals (DAAs)

The unmet therapeutic needs (~50 % for patients with genotype 1 infection) have created an intensive research activity aiming at identifying specific proteins involved in HCV cycle as therapeutic targets. New small-molecule oral inhibitors acting directly on viral targets referred as “direct acting antivirals” or DAAs have been developed and recently approved by the regulatory agencies in the US and Europe (Table 1). More specifically, these drugs target the NS3 or NS4A proteases, the NS5A and the NS5B polymerase proteins [37].

The first generation of these drugs (boceprevir, telaprevir) were used in combination with Peg-IFNa and ribavirin, leading to HCV clearance in 60–70 % of treated patients [1]. The last generation of DAAs are used either in combination with Peg-IFNa or not (“IFN-free regimens”) for 12–24 weeks and can lead to viral eradication in >90 % of the cases [1]. Their success rate depends on the viral genotype, the presence of cirrhosis, and whether patients are antiviral treatment naïve or experienced [1]. Both the American Association (AASLD) [38••] and the European Association for the Study of the

Table 1 Direct acting antiviral drugs

Medication	Approval date
NS3–NS4A protease inhibitors (PIs)	
Boceprevir	05/2011 (FDA)–07/2011 (EMA)
Telaprevir	05/2011 (FDA)–09/2011 (EMA)
Simeprevir[a]	11/2013 (FDA)–05/2014 (EMA)
Paritaprevir	
NS5A inhibitors	
Daclatasvir[a]	08/2014 (EMA)
Ledipasvir	
Ombitasvir	
NS5B polymerase inhibitors	
Nucleos(t)ide analogs	
Sofosvubir[a]	12/2013 (FDA)–01/2014 (EMA)
Non-nucleoside analogs	
Dasabuvir	
Approved DAA combinations	
Sofosvubir+ledipasvir	10/2014 (FDA)–11/2014 (EMA)
Sofosvubir+simeprevir	11/2014 (FDA)
(Paritaprevir+ombitasvir +ritonavir)+dasabuvir	12/2014 (FDA)–01/2015 (EMA)

FDA Food and Drug Administration, *EMA* European Medicines Agency

[a] In combination with Peg-IFNa, ribavirin, or their combination

Liver Diseases (EASL) [39•] have recently published specific guidelines for the best treatment options for hepatitis C.

Given their high cost, these therapies are currently prioritized for patients with advanced fibrosis or cirrhosis, transplanted patients, and patients with severe extrahepatic manifestations (including HCV-associated cryoglobulinemic manifestations) [38••].

First-Generation DAAs (Telaprevir, Boceprevir) Plus Peg-IFNa/Ribavirin In a prospective cohort study, Saadoun et al. treated 30 patients with HCV-associated CV with first-generation protease inhibitors (boceprevir or teleaprevir) and Peg-IFNa and ribavirin for 48 weeks [40••]. Almost half of the patients had received previously treatment with rituximab. Six months after the end of therapy, 67 % of patients demonstrated clinical and virological response. The improvement was more obvious for patients with purpura and arthralgias; in almost half of the patients, neuropathy also improved while renal disease improved in 5/7 patients (four had received concomitant rituximab therapy). Despite this significant clinical response, cryoglobulinemia persisted in 46 % of patients and side effects such as anemia (74 %), neutropenia (78 %), thrombocytopenia (65 %), and infections (48 %) were very common.

In a smaller study from Italy, Gragnani et al. treated five patients with symptomatic and 16 with asymptomatic cryoglobulinemia and advanced liver disease with a combination of boceprevir and Peg-IFNa and ribavirin for 48 weeks [36]. Here, the SVR was lower (0 % among symptomatic and 31 % among asymptomatic patients) and hence the clinical response transient (mainly for purpura and arthralgias) [36]. Again, anemia (60 %) and neutropenia (55 %) were frequent among treated patients. There have been also a few case reports of successful treatment of HCV-associated CV with a combination of Peg-IFNa/ribavirin and boceprevir [41, 42] or telaprevir [43]. On the contrary, in another case, combination of Peg-IFNa/ribavirin and telaprevir did not induce viral or cryoglobulin clearance in a patient with HCV-associated neuropathy [42].

Altogether, these results indicate that despite their good clinical and virological efficacy, triple antiviral therapies containing IFN and the first-generation DAAs are associated with an increased frequency of side effects in HCV patients with cryoglobulinemia.

Newer DAAs Plus Peg-IFNa/Ribavirin So far, the data regarding the newer oral antivirals are extremely limited in patients with HCV-associated CV for any definite conclusions. In a recent case series, three patients with advanced liver disease and HCV-associated CV (genotype 1) received a combination of a new DAA (sofosvubir) with Peg-IFNa and ribavirin for 12 weeks [44]. In two out of three patients, cryoglobulinemia disappeared, although neuropathy did not improve. Cornella et al. also reported three patients (genotype 1) with resistant disease to antiviral therapy with Peg-IFNa and ribavirin (one had also failed telaprevir therapy) who demonstrated viral clearance after combination therapy of Peg-IFNa/ribavirin and sofosvubir [42]. Two out of the three patients cleared also cryoglobulinemia approximately 1 month after HCV RNA clearance from the circulation [42].

Nevertheless, it should be noted that there is no clinical experience so far in patients with renal impairment who receive the new DAAs. Simeprevir and sofosvubir have no data for their use in patients with severe renal dysfunction (CrCl <30 ml/min) while the combination of paritaprevir, ombitasvir, ritonavir, and dasabuvir has not been tried in patients on hemodialysis.

Clinical Implications of Current Areas of Therapeutic Uncertainty

Given that there have not been any reports of patients with HCV-associated CV treated with "IFN-free" regimens so far, yet their effectiveness and tolerability are dramatically enhanced compared to the previous standard IFN-based regimens, clinicians are left with considerable uncertainty. For patients with mild forms of inflammatory rheumatic diseases who can afford or risk minimal therapy (i.e., non-biologic DMARDS, low-dose prednisone, etc. for 8–12 weeks), it

may be reasonable to forgo or minimize therapy and go directly to HCV therapy for 8–12 weeks in search of "curing" the underlying infection. Then treatment can be unfettered for the future. In those who cannot risk a drug-free or less intense period of therapy, even for 8–12 weeks, shared and informed discussions with the patient as to whether to risk combining therapy (i.e., DMARDS especially biologic DMARDS and DAA IFN-free regimen) may be warranted. Regardless, rheumatologists need to increase their vigilance for screening for HCV and refer all such patients for potentially "curative" therapy with IFN-free regimes. The clinical implications of the introduction of "IFN-free" regimens in the treatment of HCV-associated rheumatic diseases are obvious yet complex and are being discussed in a recent viewpoint [45].

Immunosuppressive Therapy

Monotherapy Immunosuppressive therapy with corticosteroids and/or other agents have been traditionally part of the therapeutic regimens for CV when no antiviral options were available. Low-dose corticosteroids have been used in mild to moderate HCV-associated CV, mainly for symptom control [16, 19•, 25, 26]. For severe to life-threatening disease, cyclophosphamide in the past and more recently rituximab have been used as rescue therapy with or without the addition of plasmapheresis [46].

In patients who are resistant, intolerant, or for whom antiviral therapy with IFN-based regimens is contraindicated, rituximab monotherapy has been successfully used [47, 48]. The rate of clinical response ranged from 71 to 83 % after 6 months of therapy, while for relapsing patients retreatment was efficacious [47, 48]. Caution is needed in patients with high cryocrit levels since worsening of vasculitis due to the formation of immune complexes between rituximab and IgM immunoglobulin has been reported [49].

Combination of Antiviral and Immunosuppressive Therapies It appears logical that for patients with severe or life-threatening disease, a combination of immunosuppressive therapy with antiviral therapy could be the best option. So far, there have not been any randomized controlled trials comparing antiviral therapy to antiviral therapy plus immunosuppression for this specific group of patients. More data are available from open-label studies that included approximately 100 patients where rituximab was given in addition to Peg-IFNa and ribavirin [32, 33, 50, 51]. The rate of clinical response was 69 % (ranged from 54 to 80 %). In two studies where rituximab plus antiviral therapy was compared to antiviral therapy alone, clinical response was not much different between the two groups, although patients who received additionally rituximab had a faster clinical response, improved more frequently their renal function, and the mean time to relapse was longer [32].

In general, despite the absence of controlled data, most experts suggest that for severe or life-threatening disease, immunosuppressive therapy with rituximab or cyclophosphamide is given first followed by antiviral therapy [16, 19•, 25, 26]. As mentioned earlier, there are no data with the new generation of oral DAAs given in combination with immunosuppressive therapies in such patients.

Conclusions

The recent introduction in clinical practice of the new oral antiviral agents (DAAs) for hepatitis C has paved the way for viral eradication in more than 90 % of treated patients. Furthermore, these agents can be used without IFN ("IFN-free" regimens) and thus avoiding its well-known side effects. Given the clinical efficacy of antiviral therapy with IFN-based schemes in HCV-associated rheumatic manifestations such as arthritis, sialadenitis, and more importantly CV, we expect that these agents will be efficacious and safe in these patient populations. Carefully designed studies examining their safety and efficacy in all groups of patients (with variable disease severity) though are first needed before final conclusions and recommendations can be made.

Acknowledgments Dr. Vassilopoulos' work was supported in part by research grants from the Special Account for Research Grants (S.A.R.G.), National and Kapodistrian University of Athens, Athens, Greece.

Compliance with Ethics Guidelines

Conflict of Interest Dimitrios Vassilopoulos declares the receipt of honoraria from Abbvie; Actelion Pharmaceuticals; Bristol Myers Squibb; Janssen; Merck, Sharp & Dohme; Novartis; Pfizer; Roche; and UCB.

Leonard H. Calabrese declares that he has served as a consultant for Genentech, Roche, Pfizer, Sanofi-Aventis, and Bristol-Myers Squibb, and has received honoraria from Genentech, Roche, Pfizer, Bristol-Myers Squibb, and Janssen Pharmaceutica.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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